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The relationship between paired pulse magnetic MEP and surgical prognosis in patients with intractable epilepsy

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Summary

Purpose: To assess whether paired pulse magnetic motor evoked potential (MEP) can predict surgical prognosis in patients with intractable epilepsy.
Methods: MEP of the unilateral hand muscles were recorded following paired pulse transcranial magnetic stimulation (TMS) of the motor cortex. The interstimulus intervals of paired stimulation were 1—16 ms with a conditioning stimulus that was 90% active motor threshold. Subjects were six patients with temporal lobe epilepsy (TLE) scheduled for anterior temporal lobectomy and three patients with myoclonic or head-drop seizures scheduled for anterior corpus callosotomy, resulting in the unilateralization of epileptic discharges. The hemisphere showing unilateral discharges was defined as the affected hemisphere. The intracortical inhibition and facilitation curve was drawn based on MEP before and after surgery and the relationship between MEP and surgical prognosis was investigated.
Results: In five patients with TLE showing class I surgical results (Engel's classification), the affected hemisphere showing cortical hyperexcitability preoperatively was almost normalized after surgery. However, in a patient with class III, the unaffected hemisphere showed cortical hyperexcitability before and after surgery. In the callosotomy group, two patients with excellent outcomes showed the same results as TLE group with class I.
Conclusions: Paired pulse magnetic MEP may provide predictive value in terms of surgical outcome in those patients with intractable epilepsy.

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Introduction

Epileptogenesis is due to an altered balance between excitation and inhibition in the cortex and the imbalance produces excess excitability leading to the development and spread of seizure activity. Paired pulse transcranial magnetic stimulation (TMS) is a noninvasive technique assessing the balance between neural excitation and inhibition in patients with epilepsy. Many authors have discussed the usefulness of this technique in patients with epilepsy.[2,3,5,7,8,10–12,14,15] However, there has not been any report investigating the relationship between paired pulse TMS and surgical prognosis in the patients with intractable epilepsy.

The present study assessed whether paired pulse TMS can predict the prognosis after epilepsy surgery.

Patients and methods

We studied nine patients (five males and four females: mean age 21.4, range 8–39 years old at the time of study) with intractable epilepsy (Table 1) and six healthy volunteers for the control. The patients were investigated by video–EEG recordings with additional sphenoidal electrodes, MRI and interictal single photon emission tomography (SPECT) scans using technetium-^{99m}ethyl cysteinate dimer (ECD) as a tracer. Six patients had temporal lobe epilepsy (TLE) with unilateral hippocampal sclerosis (HCS) in five and an angioma in the unilateral temporal lobe in one. Three patients had myoclonic or head-drop seizures. The former underwent anterior temporal lobectomy, while the latter received anterior corpus callosotomy (CC), resulting in the unilateralization of epileptic discharges. Mean postoperative follow-up was 16 months (range, 8–28 months). Outcomes of all patients were class I (Engel's classification) except for one patient with a class III outcome (case 6) in the TLE group. In the generalized seizure group, two of three patients had seizure reduction of more than 80%, while the remaining patient had a reduction of 50% (Table 1).

TMS was delivered by two magnetic stimulators, Magstim model 200 (Magstim Co. Ltd., Whitland, UK), coupled by a Bistim unit through a circular coil with a maximal output of 2.2 T. We used the circular coil as described in a previous study[3] because it was easier to maintain a stable point of stimulation than a figure-eight coil. The circular coil had a 90 mm outer diameter. The center of the coil was tangentially positioned over Cz and was turned over to stimulate each hemisphere favorably. All patients were seated on a chair at rest, then motor evoked potential (MEP) of the unilateral abductor pollicis brevis (APB) muscles was recorded using surface electrodes positioned over the belly muscle 3 cm apart following single test and paired pulse TMS of the motor cortex in each hemisphere. The conditioning stimulus was set to 90% active motor threshold, and the second test stimulus was adjusted to produce an unconditioned MEP of approximately 0.4–1.0 mV peak-to-peak amplitude. Single test stimuli and paired stimuli with interstimulus intervals (ISI) of 1–16 (1, 2, 3, 4, 5, 6, 8, 10, 12 and 14) ms were randomly intermingled in fairness. TMS stimulus of unilateral hemisphere was separated from other by 1 min and TMS stimuli of each hemisphere was separated by more than 5 s. TMS was not delivered until it was confirmed that background

Table 1 Clinical characteristics of patients

No.	Age (year)/sex	Seizure type	EEG	MRI	Interictal SPECT	Operation	Outcome[a]	Follow-up (month)
1	25/M	TLE	Sp, Sz: L.T	L.HCS	L.T: hypo	L.ATL	I	24
2	26/F	TLE	Sp, Sz: R.T	R.HCS	R.T: hypo	R.ATL	I	12
3	20/F	TLE	Sp, Sz: L.T	L.HCS	L.T: hypo	L.ATL	I	12
4	28/F	TLE	Sp, Sz: R.T	R.HCS	R.T: hypo	R.ATL	I	8
5	11/M	TLE	Sp, Sz: L.T	L.Angioma	L.T: hypo	L.ATL	I	12
6	25/M	TLE	Sp: B.T (L > R) Sz: L.T	L.HCS	L.T: hypo	L.ATL	III	18
7	8/M	MCS	Sp, Sz: diffuse poly S&W	Normal	R.FT: hypo	ACC	90% Disappear	28
8	39/M	HD	Sp: B.F synchronous	Normal	Normal	ACC	80% Disappear	17
9	11/F	HD, CPS	Sp: diffuse poly S&W (L < R)	Normal	Normal	ACC	50% Disappear	13

TLE, temporal lobe epilepsy; MCS, myoclonic seizure; HD, head-drop; Sp, area of interictal spike; Sz, onset of ictal discharge; HCS, hippocampal sclerosis; ATL, anterior temporal lobectomy.

[a] Engel's classification.

Table 2 Conditioned MEP values before surgery

Subjects	Values (affected hemisphere/unaffected hemisphere)											
	RT[a]	ISI 1[b]	ISI 2	ISI 3	ISI 4	ISI 5	ISI 6	ISI 8	ISI 10	ISI 12	ISI 14	ISI 16
Patients												
TLE group												
1	52/57	41/64	45/16	47/46	77/62	52/59	129/95	129/121	112/85	105/61	116/84	40/95
2	58/53	14/15	−/24	7/21	66/45	66/64	155/93	72/143	414/85	128/46	369/99	552/82
3	50/46	18/11	33/16	88/13	92/25	147/43	126/79	154/30	157/−	139/66	118/48	150/−
4	42/56	13/31	7/54	16/14	76/45	127/55	105/26	90/41	92/82	102/90	66/140	86/86
5	56/51	13/7	23/9	76/9	16/17	55/62	79/80	128/53	68/60	218/97	208/184	150/68
Mean	51.6/56.6	19.8/25.6	27.0/23.8	46.8/20.6	65.4/38.8	89.4/56.6	118.8/74.6	114.6/77.6	168.6/78.0	138.4/72.0*	175.4/111.0	195.6/82.8
S.D.	6.2/12.0	12.0/23.3	16.1/17.7	35.7/14.8	29.1/17.9	44.3/8.3	28.5/28.1	33.0/50.9	141.0/12.1	47.1/21.1	119.7/52.5	204.6/11.2
S.E.M.	2.7/5.4	5.4/10.4	8.0/7.9	15.9/6.6	13.0/8.0	19.8/3.7	12.7/12.6	14.8/22.8	63.1/6.0	21.1/9.4	53.5/23.5	91.5/5.6
6	62/76	15/82	21/68	38/105	20/180	18/300	23/319	30/294	48/280	36/100	25/150	22/109
CA group												
7	72/72	64/48	83/49	218/74	158/48	134/87	205/47	191/69	149/89	102/85	118/61	122/49
8	57/51	31/13	88/11	127/65	205/46	151/73	223/58	440/60	276/86	514/79	348/121	366/109
9	62/59	14/23	153/152	75/51	116/83	49/87	295/113	149/105	149/123	235/95	346/100	222/85
Controls												
1	68	2	8	18	56	73	48	39	91	65	34	70
2	55	18	49	54	48	54	64	100	85	129	54	86
3	58	55	49	37	58	42	91	76	114	93	121	93
4	70	46	65	86	56	177	227	170	144	100	133	146
5	68	9	57	26	49	77	103	117	38	118	124	98
6	60	34	38	46	59	76	94	162	185	186	141	265
Mean	63.2	27.3	44.3	44.5	54.3	83.2	104.5	110.7	109.5	115.2	101.2	126.3
S.D.	6.3	21.1	20	24.2	4.7	48.1	63.5	50.3	50.9	41.1	45.3	72.6
S.E.M.	2.6	6.7	9.6	11.5	10.7	23.1	29.6	27.8	21.7	16.8	18.5	29.6

RT, relaxed threshold; ISI, interstimulus intervals; TLE, temporal lobe epilepsy; CA, callosotomy; (−) not examined.

[a] RT, percentage of maximum output.

[b] ISIs, percentage of single test MEP.

* $P < 0.05$ (affected hemisphere vs. unaffected hemisphere).

activity was calm on the monitor. Filters were set from 10 Hz to 5 kHz, and the analysis time was 50 ms. The surgical side in the TLE group and the hemisphere showing unilateralized epileptic discharge in the generalized seizure group were defined as the affected hemisphere. Four trials were recorded for single test TMS and each ISI. The peak-to-peak amplitude of four MEP was measured and averaged in the controls and patients. The amplitudes of MEP obtained by the paired TMS were expressed as a percentage of MEP obtained by single test TMS and plotted against the various ISIs. MEP following single test and paired pulse TMS were recorded one month after surgery. Following the method described by Kujirai et al.[9], the intracortical inhibition (ICI) and facilitation (ICF) curve was drawn out with MEP in healthy controls and with MEP before and after surgery in patients and the relationship between MEP and surgical prognosis was investigated.

Resting motor threshold (RMT) of affected and unaffected hemispheres and intracortical inhibition and facilitation curves of affected and unaffected hemispheres in the TLE group were compared using the one-way analysis of variance with the Student—Newman—Keuls post hoc analysis (SPSS, Tokyo, Japan) before and after surgery, and differences were considered significant at a probability level equal to or less than 0.05.

We obtained informed consent from all patients or parents of the children before the study. The patients tolerated TMS without any adverse effects. TMS did not provoke seizures during or after the procedure in any patients.

Results

Comparison between affected and unaffected hemispheres in TLE and the generalized seizure groups did not demonstrate any significant differences in resting motor threshold (RMT) (Table 2).

In healthy control, conditioned MEP were inhibited at ISI of 1—5 ms and facilitated at ISI of 8—16 ms (Table 2). The graph showed ICI and ICF curve as Kujirai et al.[9] reported (data not shown).

In TLE group with class I, before surgery, there was a tendency toward less ICI at ISI 3—5 and more ICF at ISI 6—16 in the affected hemisphere than the ICI and ICF in the unaffected hemisphere. There were significant differences between affected and unaffected hemispheres at ISI 12 (Table 2, Fig. 1). After surgery, there is no difference of ICI in both hemispheres and there is a tendency of a reduction of ICF in the affected hemisphere and an increase of ICF in the unaffected hemisphere (Table 3, Fig. 1).

In a patient showing class III, before surgery, there was more ICI and less ICF in the affected hemisphere than the ICI and ICF in the unaffected hemisphere (Table 2). After surgery, the difference of ICI and ICF in both hemispheres tended to diminish but remained (Table 3).

In the generalized seizure group with excellent outcome, before surgery, there was less ICI at ISI 1—5 and more ICF at ISI 6—16 in the affected hemisphere than the ICI and ICF in the unaffected hemisphere (Fig. 2). After surgery, less ICI at ISI 1—5 and excess ICF at ISI 6—16 were not seen, or rather, the curve of the affected hemisphere was closer to the curve of the unaffected hemisphere (Fig. 2). In

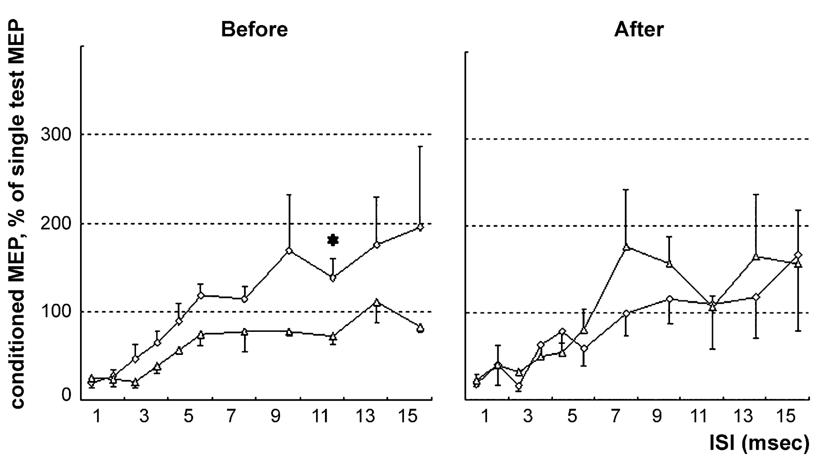

Figure 1 Intracortical inhibition (ICI) and facilitation (ICF) curves before and after surgery in five patients with temporal lobe epilepsy (TLE) of class I (Engel's classification). Bars represent S.E.M. (*Left*) Before surgery, the affected hemisphere (surgical side (◇)) showed a tendency of less ICI at ISI 3—5 and more ICF at ISI 6—16 than the unaffected hemisphere (△). There were significant differences between affected and unaffected hemispheres at ISI 12. (*Right*) After surgery, both hemispheres showed no difference of ICI and the affected hemisphere had a tendency of a reduction of ICF while the unaffected hemisphere had an increase of ICF. The symbol (*) denotes $P < 0.05$.

Table 3 Conditioned MEP values after surgery

Subjects	Values (affected hemisphere/unaffected hemisphere)											
	RT[a]	ISI 1[b]	ISI 2	ISI 3	ISI 4	ISI 5	ISI 6	ISI 8	ISI 10	ISI 12	ISI 14	ISI 16
Patients												
TLE group												
1	56/75	29/14	10/10	38/37	81/86	180/24	130/18	183/32	196/125	309/–	308/42	506/62
2	48/60	23/34	134/22	14/28	94/53	66/79	51/127	71/246	63/194	91/125	80/–	77/121
3	48/58	18/14	19/25	13/28	65/36	38/56	15/64	26/144	82/56	54/111	78/169	63/50
4	46/60	19/43	8/132	11/36	10/67	51/74	32/147	107/391	176/174	83/67	41/363	32/391
5	62/50	6/11	32/14	5/31	67/8	57/43	68/46	109/67	63/235	12/122	86/84	155/160
Mean	52.0/60.6	19.0/23.2	40.6/40.6	16.2/32.0	63.4/50.0	78.4/55.2	59.2/80.4	99.2/176.0	116.0/156.8	109.8/106.3	118.6/164.5	166.6/156.8
S.D.	6.8/9.0	8.5/14.4	53.1/51.5	12.7/4.3	32.1/29.8	57.7/22.6	44.3/54.7	57.7/145.6	64.8/68.9	115.6/26.9	107.3/142.5	195.1/138.3
S.E.M.	2.8/3.7	3.8/6.4	23.7/23.0	5.7/1.9	14.3/13.3	25.8/10.1	19.8/24.4	25.8/65.1	29.9/30.8	51.7/13.4	48.0/71.3	87.3/61.9
6	60/62	36/69	27/109	117/93	108/102	98/173	111/132	45/117	74/181	46/147	55/159	63/161
CA group												
7	70/69	77/35	41/37	37/47	36/55	64/41	94/98	53/37	90/37	39/22	48/25	24/81
8	62/62	52/121	28/105	85/119	58/92	113/109	91/68	154/125	100/112	63/118	76/33	87/96
9	62/56	92/2	114/14	95/29	82/45	82/28	58/18	156/27	179/100	222/43	127/16	95/15

RT, relaxed threshold; ISI, interstimulus intervals; TLE, temporal lobe epilepsy; CA, callosotomy.
[a] RT, percentage of maximum output.
[b] ISIs, percentage of single test MEP.

ICI and more ICF in the affected hemisphere somewhat remained after surgery (Tables 2 and 3).

Discussion

Our study suggested that the following cases could have a good postoperative outcome. (1) The TLE cases involving cortical hyperexcitability in the treated hemisphere compared with the contralateral hemisphere before surgery, tending to disappear after surgery. (2) The CC cases demonstrating marked cortical hyperexcitability of unilateral hemisphere before surgery, showed complete disappearance after surgery.

There are some reports that studied motor cortex excitability in focal epilepsies by paired pulse TMS.[3,7,16] A previous study did not analyze the results in a smaller subgroup of patients with temporal lobe epilepsy.[3] The another study could not find significant differences of motor cortex excitability between the hemisphere of epileptic focus and opposite side in untreated temporal patients using a figure-of-eight magnetic coil.[16] Moreover, Hamer et al.[7] also had the same results with a figure-of-eight magnetic coil in treated patients as the above study. Our study might have the different results from any other studies because we used a circular coil.

The present study was performed while the patients were receiving their usual antiepileptic drugs (AEDs). It has been reported by Ziemann et al. that AEDs influence TMS measures of motor excitability.[17]

In our study, TMS measures of motor excitability between the hemisphere of epileptic focus and opposite side were compared. It is unlikely that the unilaterally change of motor excitability in the present study was due to chronic intake of AEDs because AEDs tend to cause bilateral change of motor excitability.[7]

The exact neurophysiological mechanism of paired pulse TMS remains to be obscure. Paus and co-worker[14] investigated the mechanism with combined TMS/positron emission tomography (PET) approach. They speculated that suppression and facilitation of the MEP response following paired pulse TMS are mediated by different populations of interneuron in lateral premotor cortex and primary motor cortex. What might be the physiological mechanisms in cortical hyperexcitability of our TLE cases? Biella et al.[1] demonstrated that epileptiform discharges propagate along associative fibers to cortical regions that are synaptically related to the focus and speculated that this propagation may lead to the generation of secondary foci in

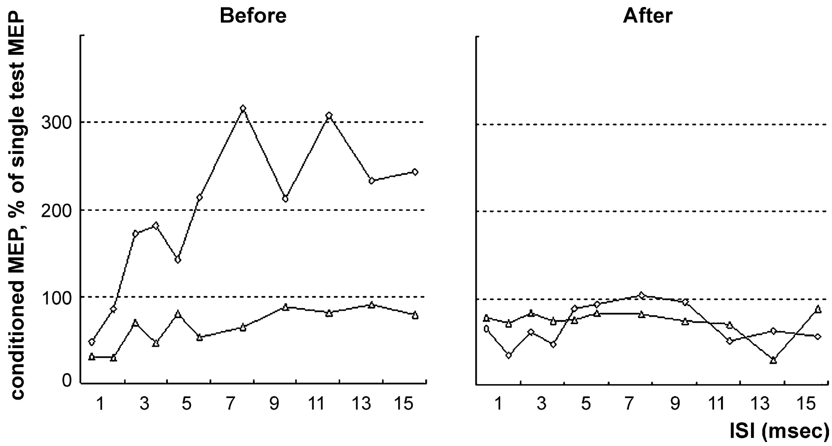

Figure 2 ICI and ICF curves before and after surgery in two patients with excellent outcome following corpus callosotomy (CC). The hemisphere showing unilateralized epileptic discharge after surgery was defined as the affected hemisphere. Bars represent S.E.M. (*Left*) Before surgery, the affected hemisphere (◇) showed less ICI at ISI 1—5 and more ICF at ISI 6—16 than the unaffected hemisphere (△). (*Right*) After surgery, the affected hemisphere showed a curve close to the unaffected hemisphere's curve (□).

cortical regions remote from the primary epileptic focus. Moreover, there are abundant associative afferent corticocortical connections between the temporal and frontal brain areas.[4,6] Therefore, it is conceivable that excitatory interneuron in primary motor cortex and surrounding frontal areas are stimulated ipsilaterally with temporal epileptogenic processes in addition to inhibition of inhibitory interneuron and that paired pulse magnetic MEP have more hyperexcitability than those of opposite hemisphere. The reason a long ISI induced more facilitation in the unaffected hemisphere after surgery may be due to the disappearance of epileptic activity transiently affecting the primary motor cortex in the contralateral hemisphere through the corpus callosum. Findings in the class III TLE case may indicate that the main epileptic activity is in a different area, for example the opposite temporal lobe, rather than the resected area.

CC has been performed in patients with intractable symptomatic generalized epilepsy or frontal lobe epilepsy which the epileptogenesis was unresectable. It has been reported that cases demonstrating interictal generalized synchronous discharges changing to unilateral discharges after surgery had excellent surgical outcomes.[13] However, it is very difficult to identify such cases preoperatively. In the present study, it was confirmed by paired pulse magnetic MEP that the hemisphere ipsilateral to the shown hemisphere with unilateral epileptic discharges after surgery had marked cortical hyperexitability preoperatively.

In conclusion, the results of the present study suggest that paired pulse magnetic MEP may provide predictive value in terms of surgical outcome in those patients with intractable epilepsy. However, our findings are based on a small population, especially in the CC group. In a future study, the relationship between paired pulse magnetic MEP and surgical prognosis should be investigated in a larger population.

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